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14. ABSTRACT

This project is to explore an innovative CAD strategy for improving early detection of breast cancer in screening mammograms by focusing on computerized analysis and detection of cancers missed by radiologists. It is motivated by the facts that (1) it can be very instructive to review retrospectively the false negative results to determine why cancers were missed in mammographic screening; (2) some preliminary studies showed that there exist distinguishing features of missed cancer which is different from that of detected cancers. Significant progresses were made on data collection and analysis of characteristics of missed caner in terms of its computational features; missed cancer analysis with a focus on density analysis and its effect on CAD detection; new CAD system design; evaluation of the stand-alone detection sensitivity/specificity of the new CAD system; evaluation of the improvement of cancer early detection by using new CAD system. The results demonstrated the effectiveness of this study in improving detection performance.

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INTRODUCTION

This project is to explore an innovative CAD strategy for improving early detection of breast cancer in screening mammograms by focusing on computerized analysis and detection of cancers missed by radiologists. Due to the unpredictable difficulty in data collection in the first year of research, a revision of the Statement of Work was made and approved by DoD to focus on the important research items.

Objective 1: ***to generate databases for missed cancer analysis and detection.***

Accomplishments:

1. Data Collection Criteria and Procedure

a. The criteria for inclusion in this study were as follows:
   1. Mass must be visible on mammogram
   2. Mass must be proven by biopsy to be malignant
   3. Mass must be seen in retrospect on a prior mammogram when reviewed by a radiologist

b. Procedure used for case selection:
   1. Lists of patients from both the screening and diagnostic centers were obtained
   2. Each patient's chart was reviewed to select for masses that were visible mammographically, all others were excluded
   3. The selected cases were reviewed for malignant pathology outcome, all others were excluded
   4. Films were requested from the diagnostic center for those cases with malignant masses
   5. Films from the screening center had to be obtained manually due to lack of manpower
   6. Films were reviewed to ascertain whether the exam and prior mammograms were available. Only those with prior mammograms were selected.
   7. Selected mammograms were reviewed by a radiologist to determine a) if the mass was visible retrospectively on the prior exam and b) the reason it was not detected on the prior exam
   8. The radiologist indicated the location and outlined the contour of the lesion on both exams and the Breast Imaging Reporting And Data System (BI-RADS) descriptors
   9. Ground truth files (hard copy) were generated based on the radiologists outlines
   10. The films were then digitized manually on a Kodak (LUMISYS) LS85 digitizer at a resolution of 50μm and 12 bits in grey scale.

2. Sources and number of cases reviewed: (as of March 23, 2004)

Query of patient databases	770
Staging database	93
Teaching files archive	148
Breast conference patients	100
Log of invasive procedures	160
Research archives	63
Total number of cases reviewed	**1,334**

3. Reasons for exclusion of cases from the original 1,334 patients reviewed:

Duplication of names among lists

Lesion was a benign mass
No pathology available
No information available for this patient/exam
No follow up for this patient
Films were unavailable or incomplete
Mass was not visible on prior mammogram (interval cancer)

a. Analysis of the 770 names from patient database queries:

Reason	**Number excluded**
Duplication of names among lists	49
Lesion was something other than a mass	337
Lesion was a benign mass	111
No information available	51
No follow up available	56

This leaves a balance of 166 potential cases, of which:

Films were unavailable or incomplete	100
Mass not visible on prior exam	16
Miscellaneous exclusions	21
Usable cases	**29**

b. Analysis of the 93 names from the staging database:

Reason	**Number excluded**
Duplication of names among lists	1
Lesion was something other than a mass	39
No information available	9

This leaves a balance of 44 potential cases, of which:

Films were unavailable or incomplete	42
Usable cases	**2**

c. Analysis of the 148 names from teaching files:

Reason	**Number excluded**
Duplication of names among lists	20
Lesion was something other than a mass	58
Lesion was a benign mass	12
No information available	13
No pathology available	1

This leaves a balance of 44 potential cases, of which:

Films were unavailable or incomplete	32
Mass not visible on prior exam	5
Usable cases	**7**

d. Analysis of the 100 names from breast conference lists:

Reason	**Number excluded**
Duplication of names among lists	8
Lesion was something other than a mass	34

Lesion was a benign mass	1
No information available	12

This leaves a balance of 45 potential cases, of which:	
Films were unavailable or incomplete	29
Mass not visible on prior exam	4
Usable cases	**12**

e. Analysis of the 160 names from invasive procedures log:

Reason	**Number excluded**
Duplication of names among lists	4
Lesion was something other than a mass	71
Lesion was a benign mass	4
No information available	20

This leaves a balance of 61 potential cases, of which:	
Films were unavailable or incomplete	34
Mass not visible on prior exam	5
Usable cases	**22**

f. Analysis of the 63 names from research archives:

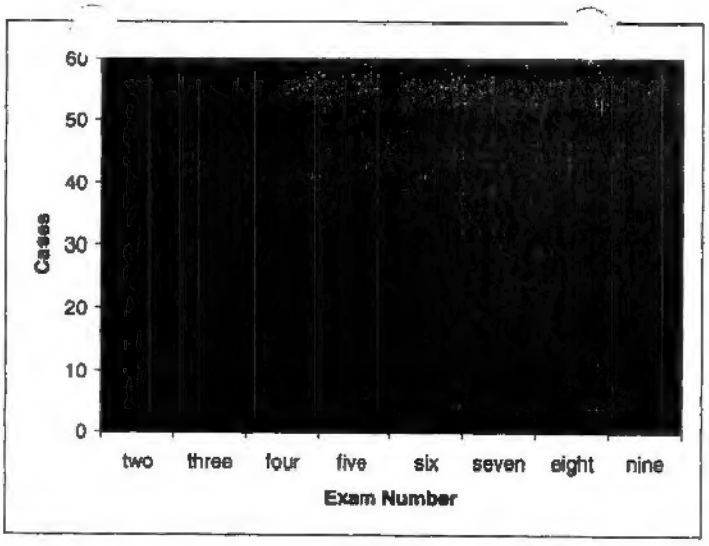
Reason	**Number excluded**
Duplication of names among lists	2
Lesion was something other than a mass	22
Lesion was a benign mass	5
No pathology available	9

This leaves a balance of 25 potential cases, of which:	
Mass not visible on prior exam	11
Usable cases	**14**

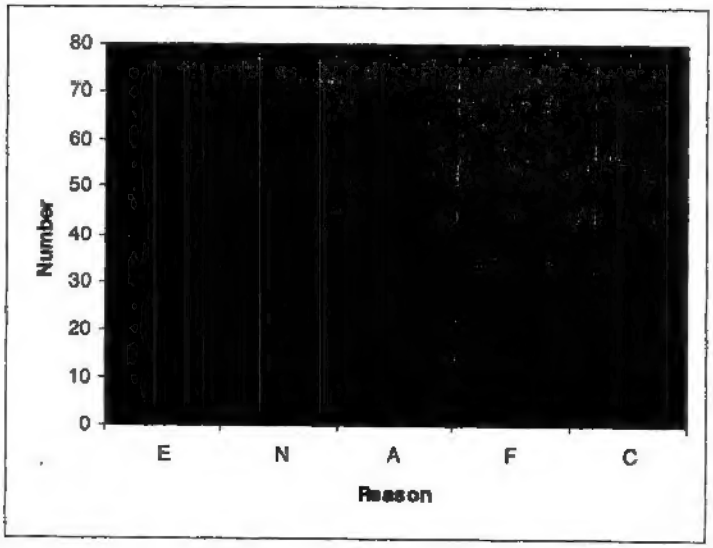
Summary: As of March 23, 2004, a total of 86 out of 1334 cases were collected as missed cancer cases for study. It is projected that there will be another 20 cases be collected before the end of May 2004, so that the total number of missed cancer cases will be more than 100.

4. Characteristic analysis of the database

The characteristics of database was analyzed by following descriptions: (a) Case distribution in terms of exam numbers, (b) Case distribution in terms of cancer missed reasons (per view and stage), (c) Case distribution in terms of mass shape, (d) Case distribution in terms of mass margin, (e) Case distribution in terms of Mass density. The histograms are shown in Figure 1.



(a)



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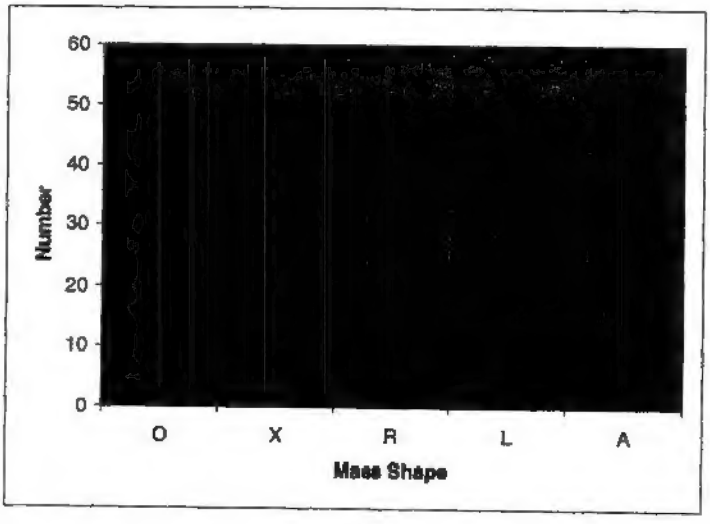
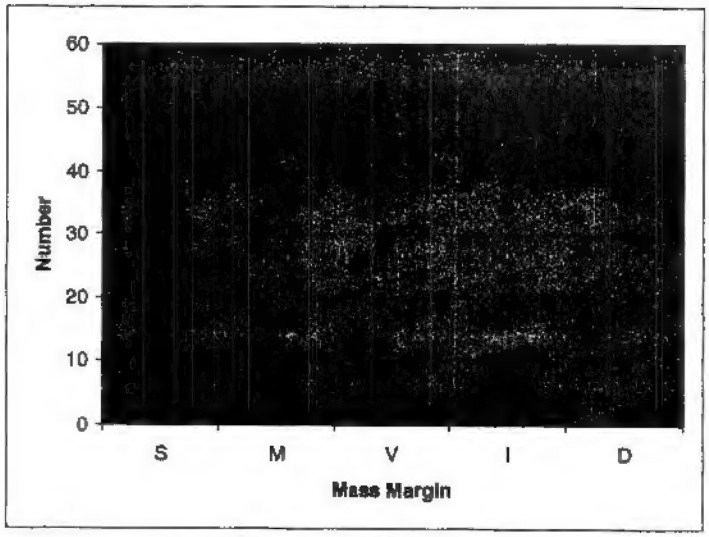
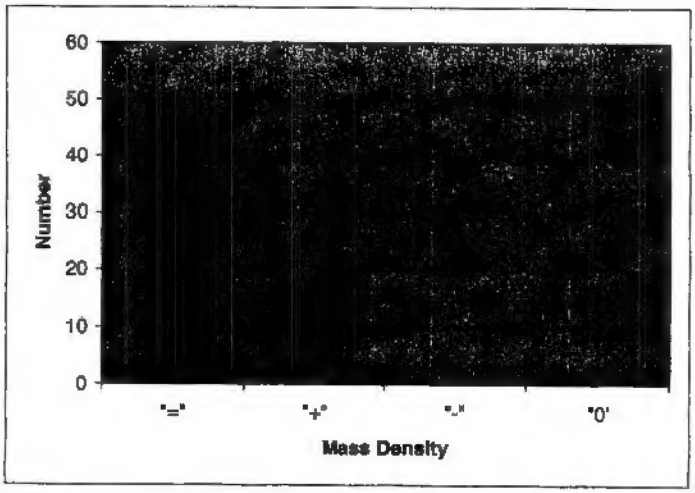


(c)



(d)



(e)

Figure 1. Case distribution in terms of (a) exam numbers, (b) missed reasons (E-interpretation error, N-not significant evidence, A-absent/no sign, F-not in field of view, C-contrast problem), (c) mass shape (O-oval, X-irregular, R-round, L-lobulated, A-architectural distortion), (d) mass margin (S-spiculated, M-microlobulated, V-obscured, I-indistinct ill defined, D-circumscribed well defined/sharply defined), (e) Mass density (=: equal/isodense, +: high, -: low, 0: fat containing/radiolucent).

Objective 2: ***to analyze the computerized features of missed cancers (false negatives) versus detected ones (true positives)***

Accomplishments:

1. Data preprocessing

There are totally 86 cases of series mammograms in the database now. Due to the

difficulty and time consuming of data collection as described above and the research timeline limitation, some preprocessing and missed cancer analysis work had to be taken in parallel with data collection. In this feature analysis study, 73 cases were processed. More and/or complete analysis will be followed. The preprocessing work for data analysis includes image format transformation (from Digital Imaging and Communications in Medicine (DICOM) format to Sun TAAC Image File Format (VFF)), image re-sampling for mass feature extraction purpose (from 50 μm to 200 μm).

2. Mass feature analysis: missed vs. detected

(1) ***ROI generation:*** Based on the mass location (center) indicated by radiologist, two sets of regions-of-interest (ROIs) are created with 256x256 pixels in size. One contains a detected mass in each ROI, the second set consists of ROIs with missed masses.

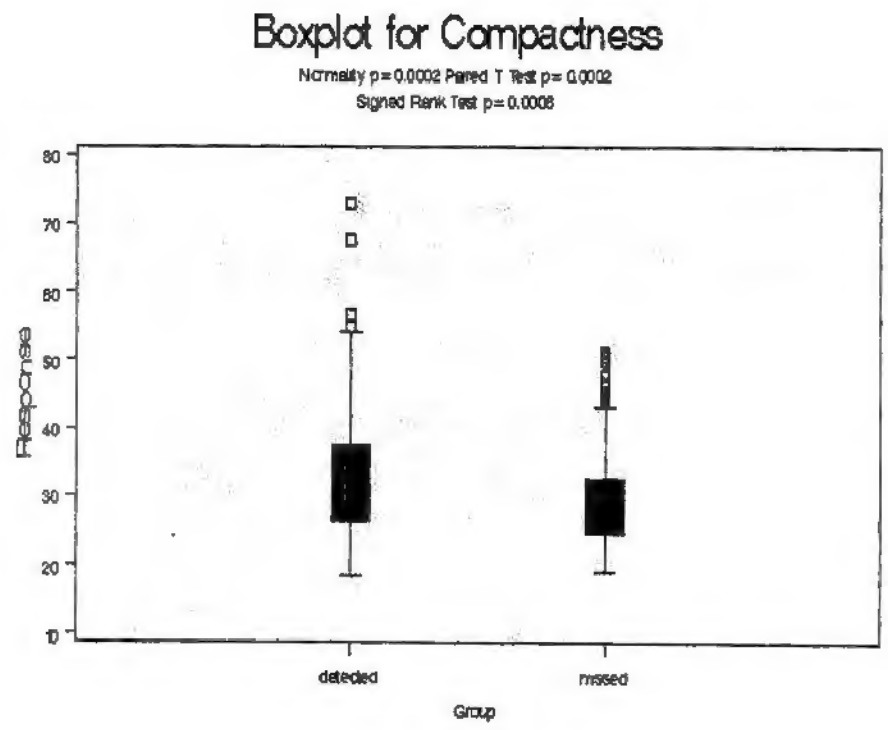
(2) ***Mass segmentation:*** Based on the ground truth (mass contour) generated by an experienced mammographer, a manual segmentation of the mass was taken by following the outline interactively with a tool we developed under Interactive Data Language (IDL) environment.

(3) ***Feature calculation:*** Following features are designed and calculated on both detected and missed masses using the original ROI image and the segmented image [1]:
Gray-level features: Intensity Mean, Intensity Variance, Intensity difference between mass area and surrounding background area;
Morphological features: Size, Circularity, Compactness, Roughness, Fluctuation, FWHM (Full-Width Half-Maximum), Radial gradient;
Texture features: Generalized Co-occurrence Matrix (GCM) based features (Energy, Difference moment, Inverse difference moment, Correlation), Laws features.

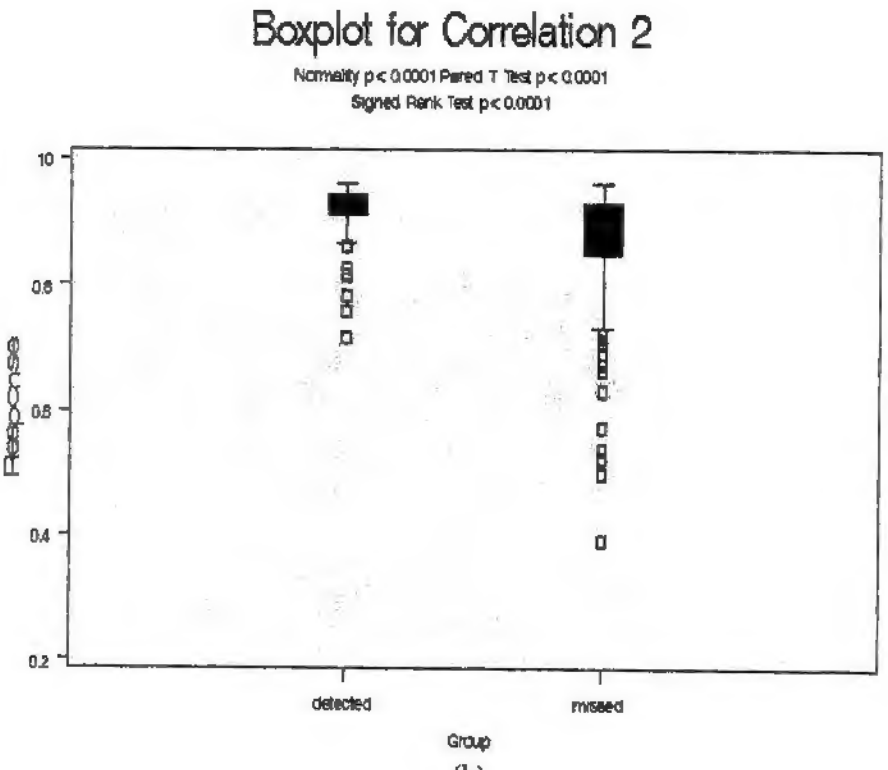
(4) ***Statistical analysis:*** To explore the difference of detected and missed cancer features, a set of tests was applied to the extracted features individually. Listed in Table 1 are the *p*-values of three tests including normality test, paired t-test, and signed rank test for each feature [2]. In order to explore the potential effect of mammography exam view on interpretation and the difference of missed cancer features on different views, in addition to the Craniocaudal (CC) and Mediolateral Oblique (MLO) combined test, statistical tests on CC view only and MLO view only were also taken. Following is the interpretation of test results:

- If normality p-value is less than 0.05, we say the difference between miss and detection of certain feature is not normally distributed.
- If the difference between miss and detection of certain feature is normally distributed, we use paired t-test. If t-test P-value is less than 0.05, we have evidence to reject null hypothesis that the mean of difference is zero at significant level 0.05. (significantly different)
- If the difference between miss and detection of certain variable is not normally distributed, we use signed rank test. If signed rank test P-value is less than 0.05, we have evidence to reject null hypothesis that the mean of difference is zero at significant level 0.05. (significantly different)
- From the table, the most significantly changed features are size, intensity variance, intensity difference, compactness, correlations, difference entropy, and inverse difference moments.

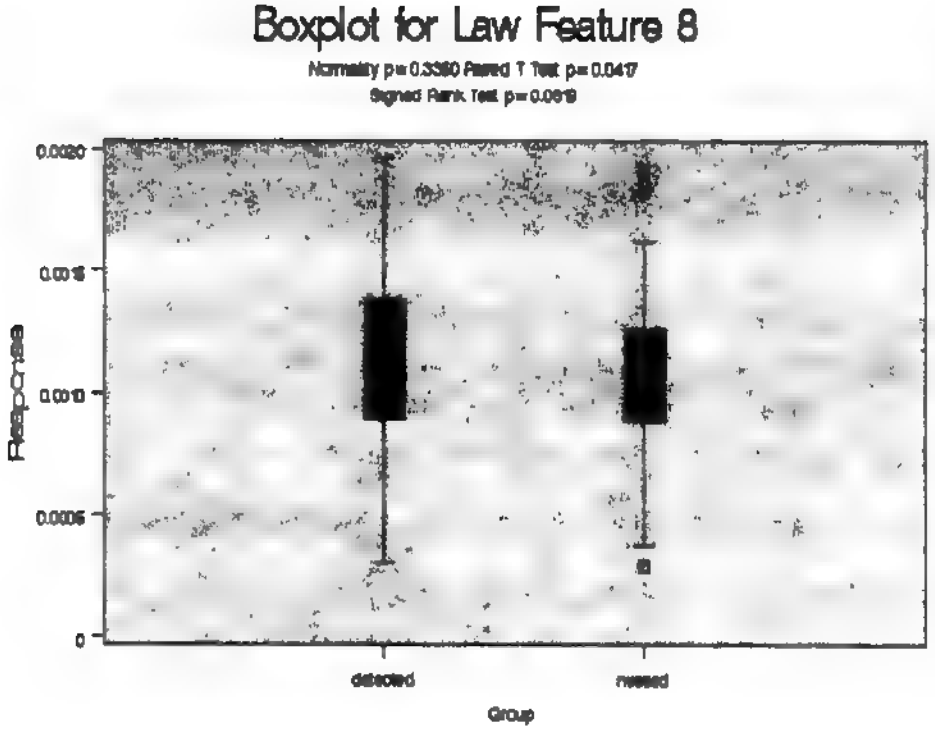
For illustrative purpose, box-plots of four features are shown in Figure 2. It is observed that the features of Compactness and Correlation 2 (at 45 degree) have a significant difference between the detected and missed masses, while there are not statistical difference in terms of Laws Feature 8 and intensity Mean.


Boxplot for Compactness
Normality p=0.0002 Paired T Test p=0.0002
Signed Rank Test p=0.0008
Response
80
70
60
50
40
30
20
10
detected
missed
Group

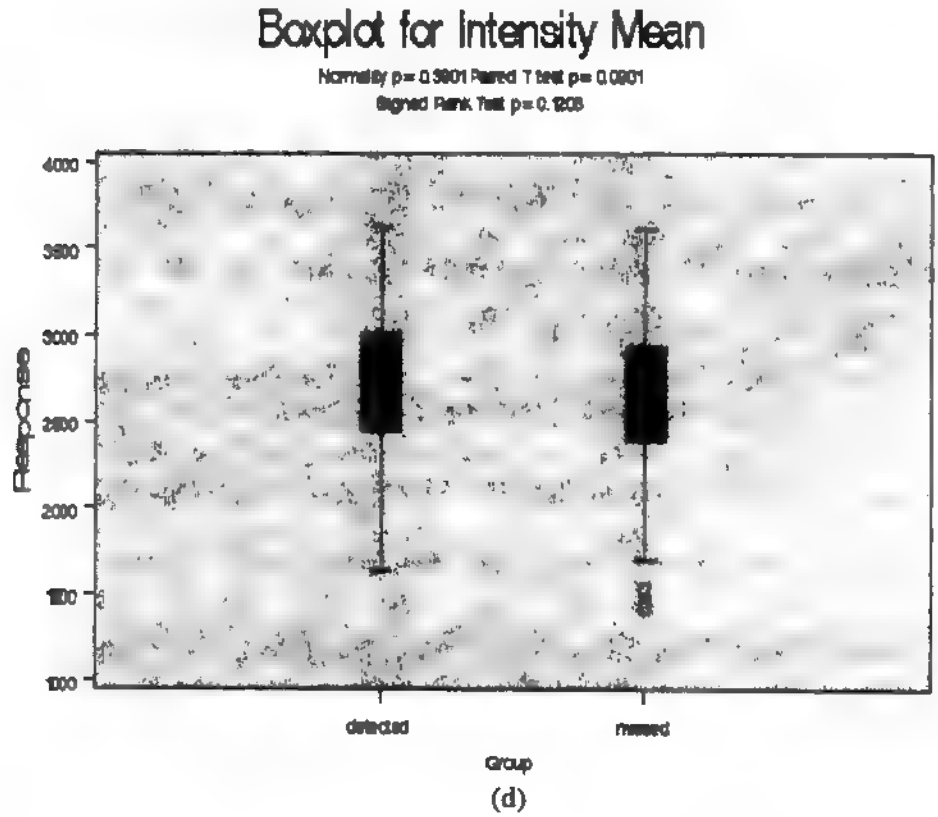
(a)


Boxplot for Correlation 2
Normality p< 0.0001 Paired T Test p< 0.0001
Signed Rank Test p< 0.0001
Response
1.0
0.8
0.6
0.4
0.2
detected
missed
Group

(b)



(c)



(d)

Figure 2. Box-plots for the illustration of statistical tests of the difference of four computerized features between missed and detected cancers.

3. Breast density analysis

(1) The breast area in a mammogram is segmented from the surrounding background. The chest wall is removed by manual segmentation. Based on the characteristic features of the gray level histogram of breasts at different intensity level, a gray level threshold value for each image is determined by interactive method to segment the dense area from the breast. Four classes can be classified according to a gray level histogram of the breast area. A typical Class I is almost entirely fat, it has a single narrow peak on the histogram. Class II has scattered fibroglandular densities. It has two peaks. The smaller peak is on the right of the bigger one. Class III is heterogeneously dense. It has two peaks, but the smaller peak is on the left of the bigger one. Class IV is extremely dense, which has a single dominant peak on the histogram, but it is wider compared with the peak in the Class I histogram.

(2) The area of segmented dense tissue as a percentage of the breast area is then calculated as the index of breast density.

(3) A preliminary study was taken to analyze the breast density feature of missed cancer cases versus detected cases. The p-values of statistical test are listed in Table 1.

4. Temporal Analysis

Temporal analysis was taken to explore the difference of characteristics between the changes of features among normal region, missed cancer region and detected cancer region. Following features of each ROI are calculated [1]: (1) Intensity Mean, (2) Intensity Variance, (3) Energy, (4) Difference Moment, (5) Inverse Difference Moment, (6) Correlation, and (7) 14 Laws features. Listed in Table 1 are the *p*-values of three tests including normality test, paired t-test, and signed rank test for each feature [2].

Table 1. P-Value Table: Missed vs. Detected

FEATURE NAME	VIEW	NORMALITY	PAIRED T TEST	SIGNED RANK TEST
Size	CC & MLO	<0.0001	<0.0001	<0.0001
	CC	0.0017	<0.0001	<0.0001
	MLO	<0.0001	<0.0001	<0.0001
Intensity Mean	CC & MLO	0.3901	0.0901	0.1206
	CC	0.3430	0.1864	0.2675
	MLO	0.9198	0.2961	0.3102
Intensity Variance	CC & MLO	<0.0001	<0.0001	<0 0001
	CC	0.9714	<0.0001	<0.0001
	MLO	<0.0001	<0.0001	<0.0001
Intensity Difference	CC & MLO	0.0020	<0.0001	<0.0001
	CC	0.0039	<0.0001	<0.0001
	MLO	0.2125	<0 0001	<0.0001
Circularity	CC & MLO	0.0058	0.2910	0 3514
	CC	0.2054	0.8544	0.9941
	MLO	0.0035	0.1815	0.1485
Compactness	CC & MLO	0.0002	0.0002	0.0006
	CC	0.0033	0.0026	0.0046
	MLO	0 0056	0.0239	0.0435
Roughness	CC & MLO	0.9990	0.7341	0.7418
	CC	0.8514	0.8370	0.7942
	MLO	0.9171	0.7785	0.8501

Fluctuation	CC & MLO	0.0305	0.397	0.2200
	CC	0.0662	0.5970	0.3196
	MLO	0.0376	0.5091	0 5457
FWHM	CC & MLO	0.1922	0.8510	0.9160
	CC	0.3860	0.4120	0.3616
	MLO	0.1507	0 2451	0.4618
Radial Gradient	CC & MLO	0.0953	0.5127	0.3446
	CC	0.4060	0.2434	0.2047
	MLO	0.3737	0.8030	0 9189
Energy 1 (0°)	CC & MLO	<0.0001	0.3936	0.9370
	CC	<0.0001	0.5053	0.8580
	MLO	0.0004	0.5975	0.9652
Energy 2 (45°)	CC & MLO	<0.0001	0.6619	0.5762
	CC	<0.0001	0.6952	0.6120
	MLO	0.0002	0.8280	0.7991
Energy 3 (90°)	CC & MLO	<0.0001	0 4716	0.7709
	CC	<0.0001	0.5435	0.7656
	MLO	0.0001	0.6921	0.9247
Energy 4 (135°)	CC & MLO	<0.0001	0.6684	0.5407
	CC	<0.0001	0.6988	0.6015
	MLO	0.0001	0.8333	0.7712
Difference Moment 1 (0°)	CC & MLO	<0.0001	0.3298	0.0118
	CC	0 0048	0.3024	0.0721
	MLO	<0.0001	0.6863	0.0721
Difference Moment 2 (45°)	CC & MLO	<0.0001	0.6844	0.0518
	CC	0.0141	0.5397	0.2302
	MLO	<0.0001	0.9612	0.1159
Difference Moment 3 (90°)	CC & MLO	<0.0001	0.3230	0.0197
	CC	0.0028	0.2845	0.0525
	MLO	0 0010	0.6655	0.1706
Difference Moment 4 (135°)	CC & MLO	<0.0001	0.5049	0.0151
	CC	0.0002	0.4790	0.0733
	MLO	<0.0001	0.7580	0.1075
Inverse Difference Moment 1 (0°)	CC & MLO	0.5219	0.0006	0.0002
	CC	0 9513	0.0289	0.0232
	MLO	0.4463	0.0076	0.0024
Inverse Difference Moment 2 (45°)	CC & MLO	0.3035	0.0038	0.0010
	CC	0.9965	0.0601	0.0516
	MLO	0.1456	0.0264	0.0062
Inverse Difference Moment 3 (90°)	CC & MLO	0.0132	0.0019	0.0002
	CC	0.1402	0.0451	0.0151
	MLO	0.1016	0.0168	0.0040
Inverse Difference Moment 4 (135°)	CC & MLO	0.0402	0 0029	0 0004
	CC	0.0916	0.0490	0.0154
	MLO	0.2635	0.0272	0.0135
Correlation 1 (0°)	CC & MLO	<0.0001	<0.0001	<0.0001
	CC	<0.0001	0.0134	<0.0001
	MLO	<0.0001	<0.0001	<0.0001
Correlation 2 (45°)	CC & MLO	<0.0001	<0.0001	<0.0001
	CC	<0.0001	0.0006	<0.0001
	MLO	<0.0001	<0.0001	<0.0001
Correlation 3 (90°)	CC & MLO	<0.0001	<0.0001	<0.0001
	CC	<0.0001	0.0152	<0.0001
	MLO	<0.0001	<0.0001	<0.0001

	CC & MLO	<0.0001	<0.000	<0.0001
Correlation 4 (135°)	CC	<0.0001	0 0033	<0.0001
	MLO	<0.0001	<0.0001	<0.0001
Laws Feature 1	CC & MLO	<0.0001	0.0337	0.0373
	CC	<0.0001	0 0970	0.0506
	MLO	0.4194	0.1912	0.3280
Laws Feature 2	CC & MLO	<0.0001	0.0866	0.0167
	CC	<0.0001	0.1364	0.0575
	MLO	0.0001	0.4029	0.1571
Laws Feature 3	CC & MLO	<0.0001	0.0856	0.0146
	CC	<0.0001	0.1356	0.0488
	MLO	<0.0001	0.3971	0.1485
Laws Feature 4	CC & MLO	<0.0001	0.0574	0.0484
	CC	<0.0001	0.0973	0.1425
	MLO	0.0712	0.3605	0.2218
Laws Feature 5	CC & MLO	0.5129	0.0841	0.0872
	CC	0.4619	0.2403	0.1838
	MLO	0.5717	0.2095	0.2963
Laws Feature 6	CC & MLO	0.0088	0.0346	0.0466
	CC	0.0028	0.1446	0.1383
	MLO	0.4038	0.1275	0.2081
Laws Feature 7	CC & MLO	0.0015	0.0275	0.0399
	CC	0.0010	0.1419	0.1692
	MLO	0.3080	0.0976	0.1464
Laws Feature 8	CC & MLO	0.3350	0.0417	0.0819
	CC	0.2689	0.1936	0.2515
	MLO	0.4877	0.1144	0.1899
Laws Feature 9	CC & MLO	<0.0001	0.0245	0.0299
	CC	<0.0001	0.1294	0.1404
	MLO	0.3082	0.0866	0.1195
Laws Feature 10	CC & MLO	<0.0001	0.0290	0.0509
	CC	<0.0001	0.1487	0.1941
	MLO	0.2991	0.0892	0.1527
Laws Feature 11	CC & MLO	0.0623	0.0539	0.1032
	CC	0.0550	0.2385	0.3196
	MLO	0.4846	0.1169	0.1729
Laws Feature 12	CC & MLO	<0.0001	0.0398	0.0862
	CC	<0.0001	0.1875	0.2911
	MLO	0.2861	0 0989	0.1777
Laws Feature 13	CC & MLO	0.1695	0.0630	0.0976
	CC	0.1234	0.2750	0.3159
	MLO	0 6673	0.1186	0.1660
Laws Feature 14	CC & MLO	0.6084	0.0839	0.0800
	CC	0.5726	0 3567	0.2842
	MLO	0.7555	0.1242	0.1108
Density	CC & MLO	0.0085	0.0230	0.3594
	CC	0.0413	0.5366	0 8522
	MLO	0.0946	0.0073	0.0199

Table 2 Temporal Comparison

FEATURE NAME	Normality	Paired T-Test	Signed Rank Test
Intensity Mean	0.8584	0.0099	0.0069
Intensity Variance	0.1426	0.4962	0.3167
Energy 1 (0°)	0 9759	0.9445	0.8176
Energy 2 (45°)	0.9510	0.9592	0.8332
Energy 3 (90°)	0 9791	0.9562	0.8176
Energy 4 (135°)	0.9808	0.9378	0.8020
Difference Moment 1 (0°)	0.9001	0.4837	0 5001
Difference Moment 2 (45°)	0.3719	0.6939	0.6806
Difference Moment 3 (90°)	0.9847	0.3220	0.3799
Difference Moment 4 (135°)	<0.0001	0.3010	0.6513
Inverse Difference Moment 1 (0°)	0.9352	0.5495	0.6083
Inverse Difference Moment 2 (45°)	0.8829	0.8537	0 9441
Inverse Difference Moment 3 (90°)	0.8287	0.4730	0.4622
Inverse Difference Moment 4 (135°)	0.7900	0.4166	0.4378
Correlation 1 (0°)	<0 0001	0.2298	0.1328
Correlation 2 (45°)	<0.0001	0.2983	0.1274
Correlation 3 (90°)	0.0051	0.3962	0.2050
Correlation 4 (135°)	<0.0001	0.1911	0.1383
Laws Feature 1	<0.0001	0.3688	0.2075
Laws Feature 2	0.0107	0.0557	0.0152
Laws Feature 3	0.0007	0.1023	0.0196
Laws Feature 4	0.0443	0.0350	0.0140
Laws Feature 5	<0.0001	0.7859	0.0886
Laws Feature 6	<0.0001	0.1694	0.5749
Laws Feature 7	0.0037	0.0171	0 0067
Laws Feature 8	0.0008	0.0346	0.0151
Laws Feature 9	<0.0001	0.0753	0.0067
Laws Feature 10	0.0011	0 3924	0.0554
Laws Feature 11	0.2971	0 0058	0.0067
Laws Feature 12	<0.0001	0.3370	0.0215
Laws Feature 13	<0.0001	0.0952	0.0067
Laws Feature 14	0.2214	0.0033	0.0015

Objective 3: ***to determine the effect of density pattern on cancers detection***

Accomplishments:

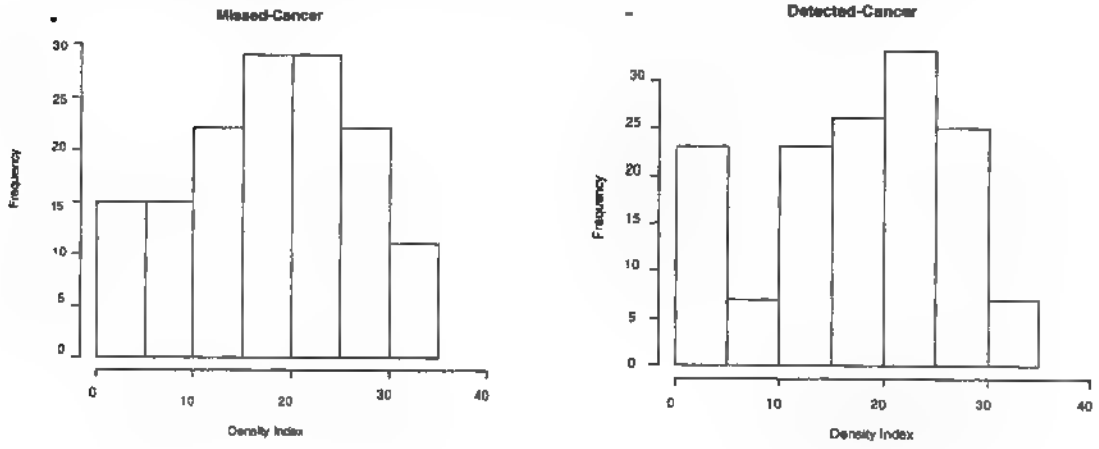
(1) Segmentation of glandular regions in mammogram

An automatic approach was applied in mammographic dense tissue segmentation. It is a statistical-based method developed in our lab [1]. The segmentations were taken on both cancerous and normal mammograms at screening-detected and screening-missed stages respectively. The percentage of segmented density tissue area out of the whole breast area is calculated as the index of breast density. Figure 1 shows the histograms of density index of three

different type mammograms. To check the correlation of density between mammograms at missed and detected stages, two kinds of correlation analysis, i.e. Pearson's correlation and Spearman's Rank correlation, were taken [2]. The Pearson correlation coefficient measures the strength and direction of a *linear* relationship between two variables. One problem is that if there are outliers in the data, Pearson's correlation coefficient will be greatly affected. Also, Pearson's correlation coefficient only measures linear relationships between variables. Spearman's rank correlation coefficient is a nonparametric (distribution-free) rank statistic which is a measure of strength of the associations between two variables. As this measure depends only on ranks it is not affected by outliers. The correlation coefficients are listed in Table 1. It is observed that (i) there is a good consistency between the Pearson's correlation and Spearman's Rank correlation, i.e. no significant outliers exist in density segmentation; (ii) the breast density segmented at missed stage is correlated to that at detected stage; (iii) the segmentation correlation between normal mammograms at missed and detected stages is higher than that with cancerous mammograms. An explanation is that the cancerous mammogram usually has more complicated density pattern and is statistically of higher density as shown below, which makes big variations in segmentation.

Table 1. Correlation of Density Segmentation.

Variable 1	Variable 2	Pearson's correlation coefficients	Spearman's correlation coefficients
Missed_cancer	Detected_cancer	0.5896	0.5946
Missed_normal	Detected_normal	0.6908	0.6882



(a) (b)

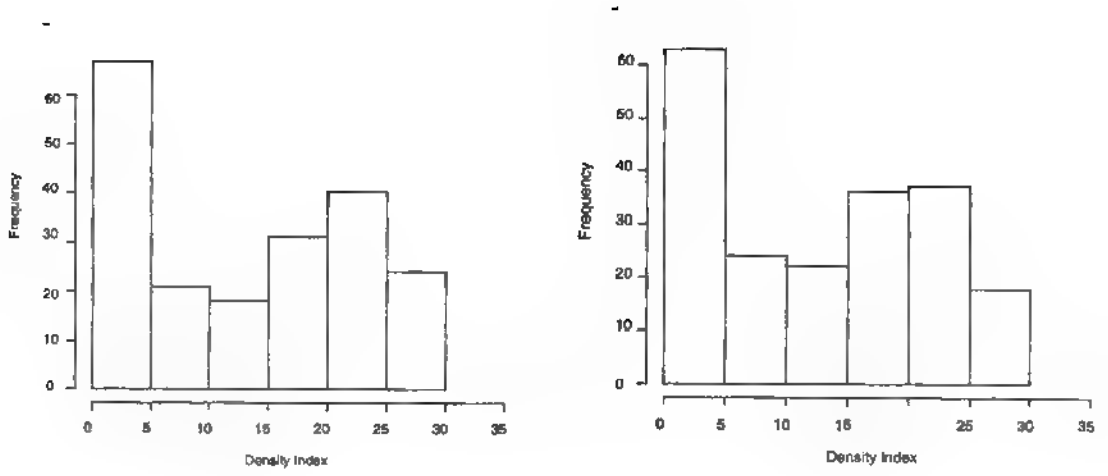


Figure 1. Histograms of breast density: (a) cancerous mammogram at missed stage; (b) cancerous mammogram at detected stage; (c) normal mammogram at missed stage; (d) normal mammogram at detected stage.

(2) Density analysis of normal and cancerous mammograms

A set of statistical testing was taken to exam (i) Is there any difference in density between the mammograms at the detected stage and that at missed stage? (ii) Is there any difference in density between the normal mammograms and the cancerous mammograms? Listed in Table 2 are the p-values of T-test and Wilcoxon rank test for density difference between detected stage mammogram and missed stage mammogram, and the normal mammogram and cancerous mammogram respectively. If the difference of density index is normally distributed, we use t-test otherwise use Wilcoxon rank test. If the test p-value is less than 0.05, we have evidence to reject null hypothesis that the mean of difference is zero at significant level 0.05, i.e. significantly different [2]. It is observed that (i) there is no significant change in density of mammograms at detected and missed stages for both the normal and cancerous mammograms. It is because most of the mammograms at missed and detected stages were taken in consecutive years as shown in Figure 2, during which no significant change could have happened on breast. (ii) There is a significant difference in density between normal and cancerous mammograms at both detected and missed stages. Specifically the cancerous mammograms have a higher density than normal mammograms.

Table 2. Statistical Test of Density Difference

Variable 1	Variable 2	T– test p-value	Wilcoxon test p-value
Missed_cancer	Detected_cancer	0.4793	0.5919
Missed_normal	Detected_normal	0.6708	0.5326
Missed_cancer	Missed _normal	5.977e-07	3.339e-06
Detected_cancer	Detected_normal	2.579e-06	5.067e-06

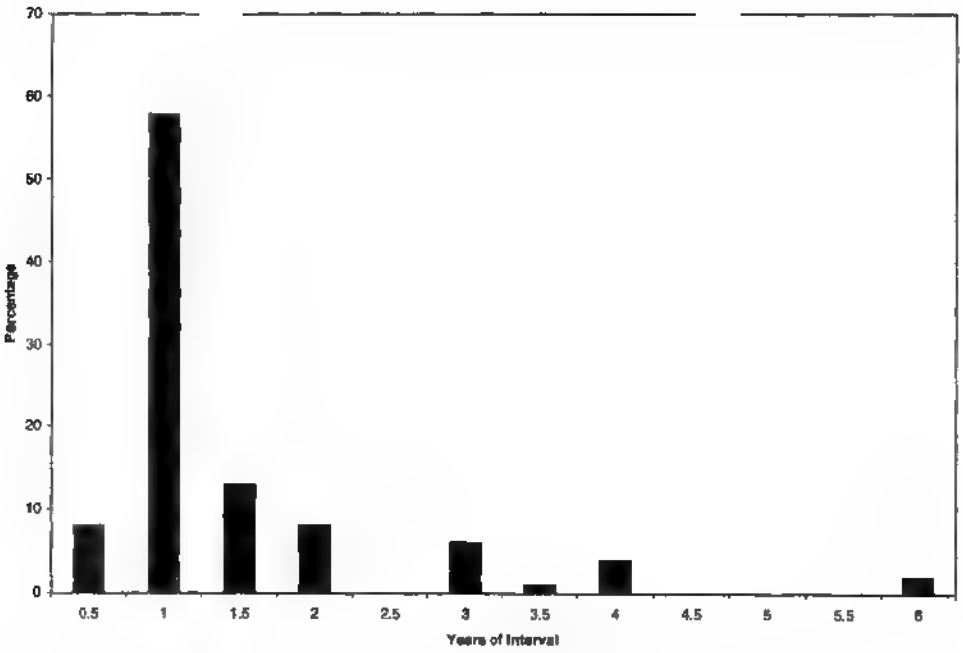


Figure 2. A distribution of interval between mammograms taken at missed and detected stages.

(3) Effect of density pattern on CAD detection performance

In the study described above, we have demonstrated the statistical difference in breast density between the normal and cancerous mammograms. It has also been reported that the lesions occurred in dense breasts are statistically more likely to be missed in screening mammogram [3]. However there is no report on study of the effect of density on CAD detection performance. In this research, as a baseline study, we used our existing CAD algorithm for detection testing on the serial database with an intention to examine the differences in detection performance for cases with different breast density. The detailed technical information on the CAD algorithm can be found in [4][5]. Due to the limited size of database, the mammograms were classified into two categories corresponding to density percentages of less or more than 25%. Figure 2 and 3 show the FROC curves of CAD detection results of high (>25%) and low (<25%) density cases at missed and detected stages respectively. It is observed that (i) the detection performance on less dense case is better than that on high dense cases. In other words, similar to the radiologists in mammogram screening, the lesions occurred in dense breasts are more likely to be missed in CAD detection; (ii) the difference of detection performance between high and low dense cases is smaller at the detection stage than that at missed stage, i.e. the lesions on dense mammograms are even more difficult to detect compared to the lesions on low dense mammograms at the missed stage.

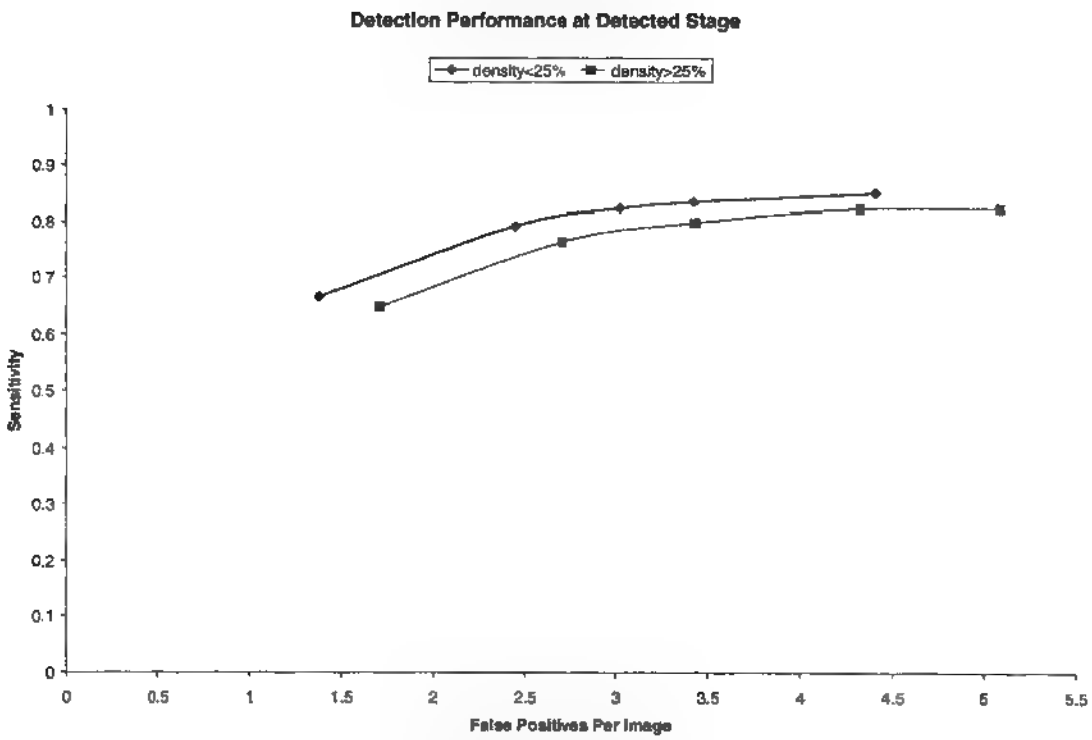


Figure 3. FROC curves of CAD cancer detection on mammograms at screening detected stage.

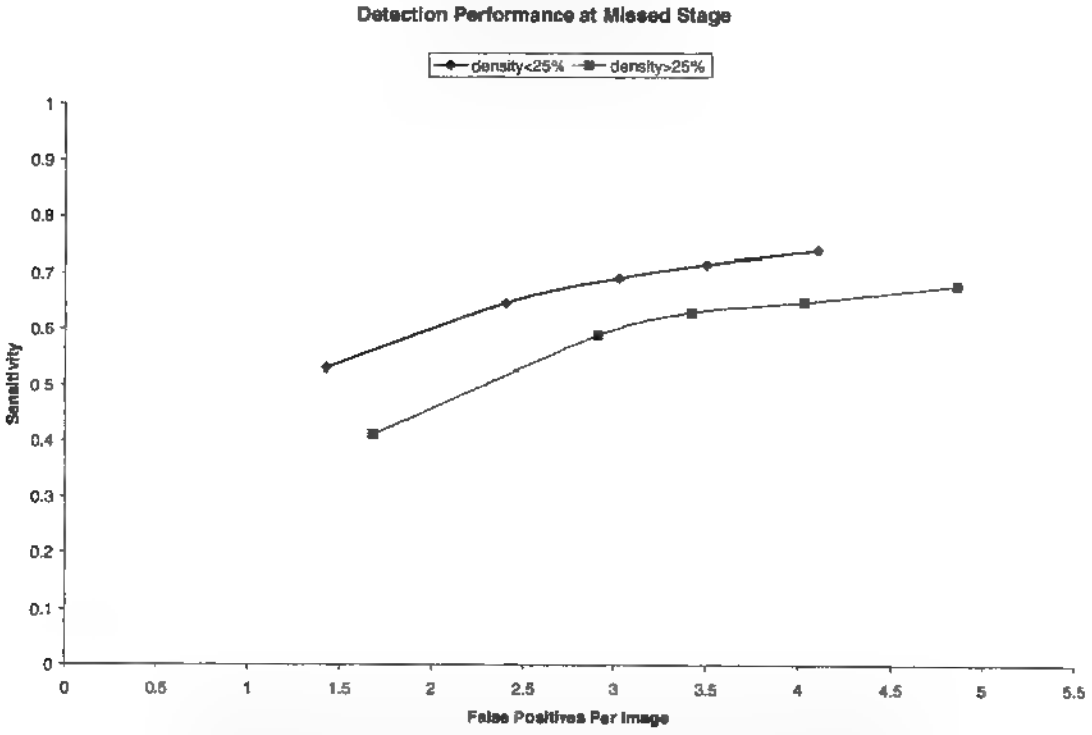
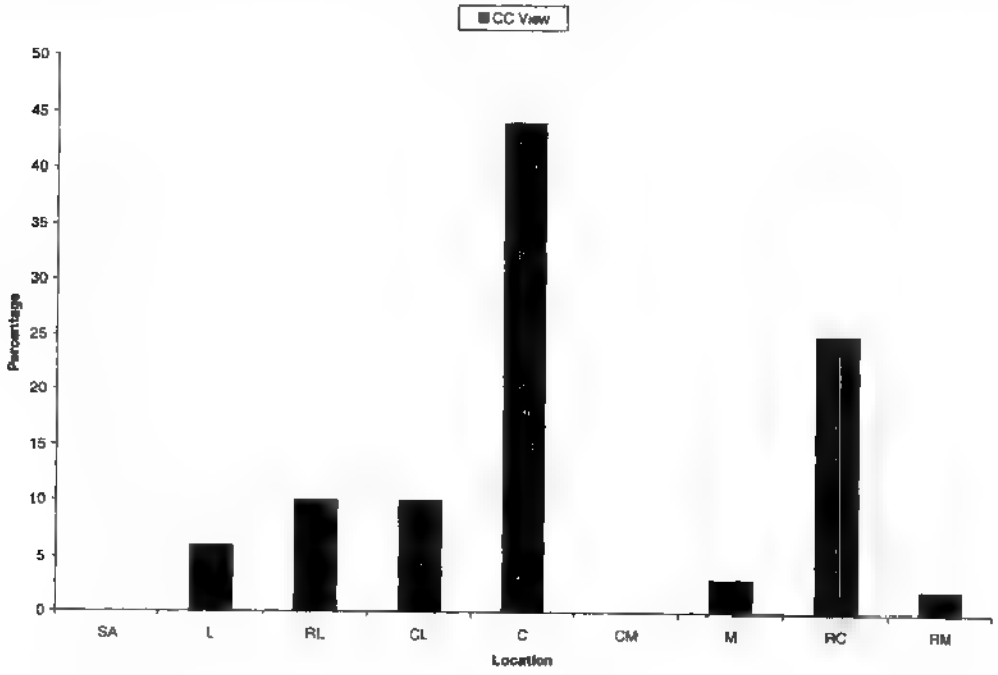


Figure 4. FROC curves of CAD cancer detection on mammograms at screening missed stage

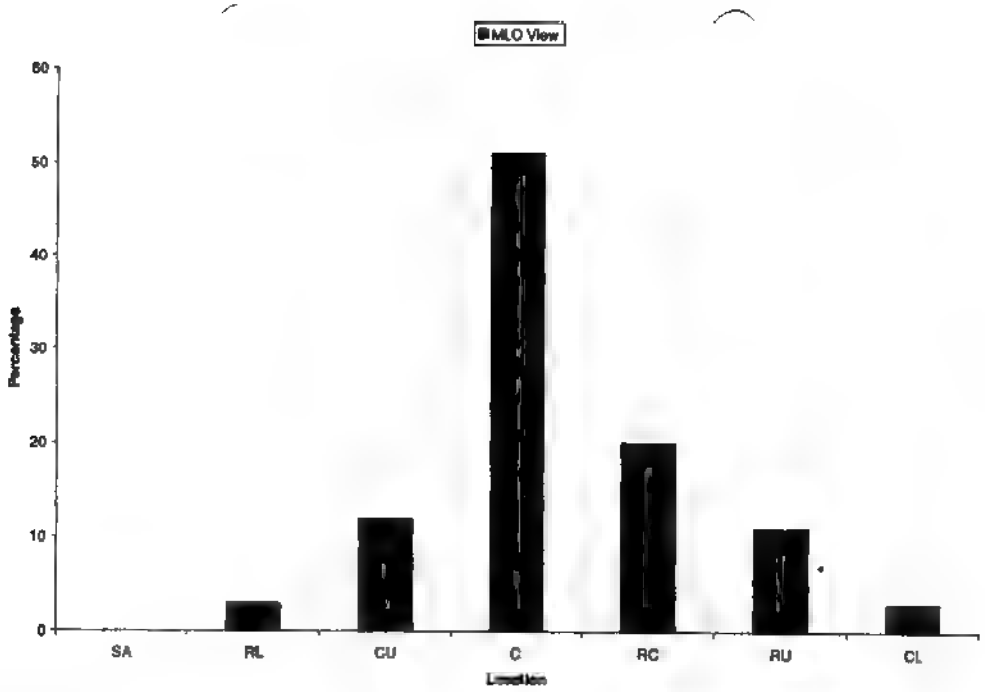
Objective 4: to design new CAD system for improving missed cancer detection

Accomplishments:

The new CAD system is based on our two generations of CAD algorithms for mass detection using digitized mammogram [4][5] and incorporates the analysis results of missed cancer in the design. The strategies taken in this study include *(a) Multi-mode detection by breast density classification:* It has been demonstrated in the baseline testing study by using existing CAD algorithm that the lesions occurred in dense breasts are more likely to be missed in CAD detection. Therefore, in order to improve the detection of missed cancer, a multi-mode detection was performed by classifying the mammogram with breast density index as defined above before an appropriate detection mode is applied to the detection. Due to the limit size of database in this study, each input mammogram was classified into two categories corresponding to density percentages of <25% and >25%. *(b) Breast area partition and region based adaptive detection*: Due to the fact that the location of cancer appearance in mammograms has a big variation in missing probability in screening mammogram, breast area partition provides the basis for further adaptive processing. The partition process consists of three steps: (i) breast boundary and nipple detection; (ii) pectoral muscle and view (CC or MLO) identification; (iii) area partition. Figure 5 shows the likelihood of missed cancers in each region. *(c) Weighted classification using the distinguishing features identified in missed cancer analysis*: The classification is a modified hybrid structure in which (i) a combined "hard" and "soft" decision classification strategy was applied [4][5]; (ii) decision thresholds were adjusted based on the missed cancer feature analysis. For example, a significant difference in feature "mass size" was observed between detected and missed stages, therefore the threshold for this feature in decision tree was reduced in order to enhance the chance of missed cancer to be detected; (iii) candidate competition are weighted using region likelihood value. Figure 7-11 show the FROC curves of detection on mammograms of missed and detected cancer stages. It is observed that the new CAD system provides a better detection performance at both missed and detected stages. However, because the new CAD is designed with focus on missed cancer, a bigger improvement is obtained for missed cancer detection.



(a)



(b)

Figure 5. Distribution of cancers at different locations on (a) CC view and (b) MLO view, where SA=Subareol, C=Central, CL=Lower-Central, CU=Upper-Central, RC=Central-Retroglandular, RU=Upper-Retroglandular, RL=Lower-Retroglandular, L=Lateral, CL=Central-Lateral, CM=Medial-Central, RM=Medial-Retroglandular, RL=Lateral-Retroglandular.

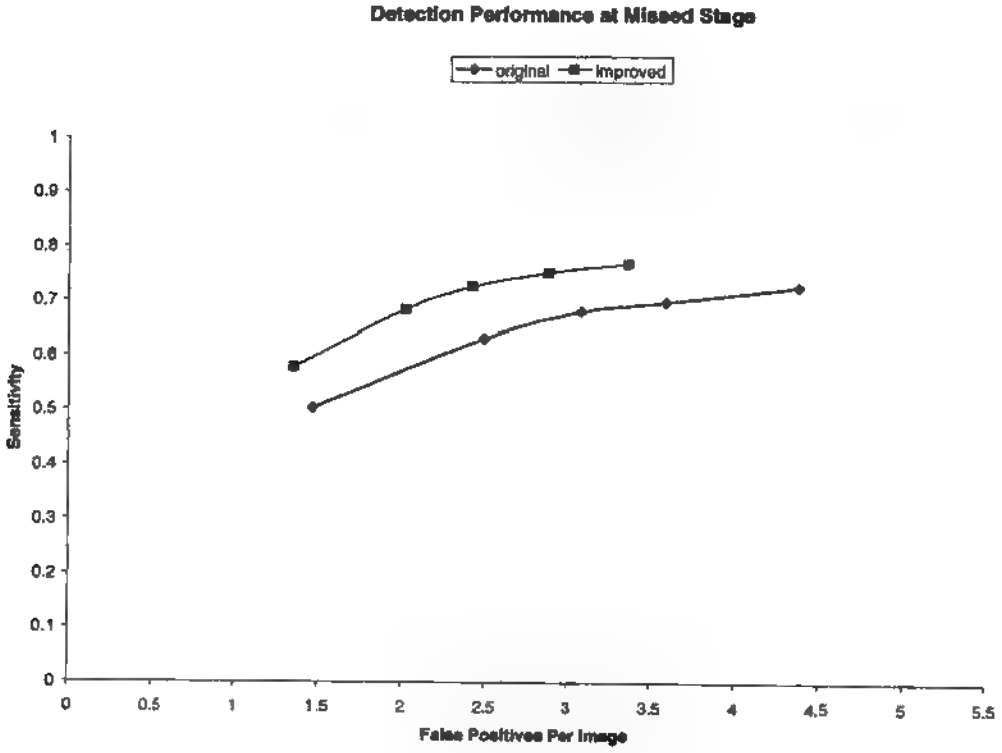


Figure 6. Improvement of CAD cancer detection on mammograms at screening missed stage.

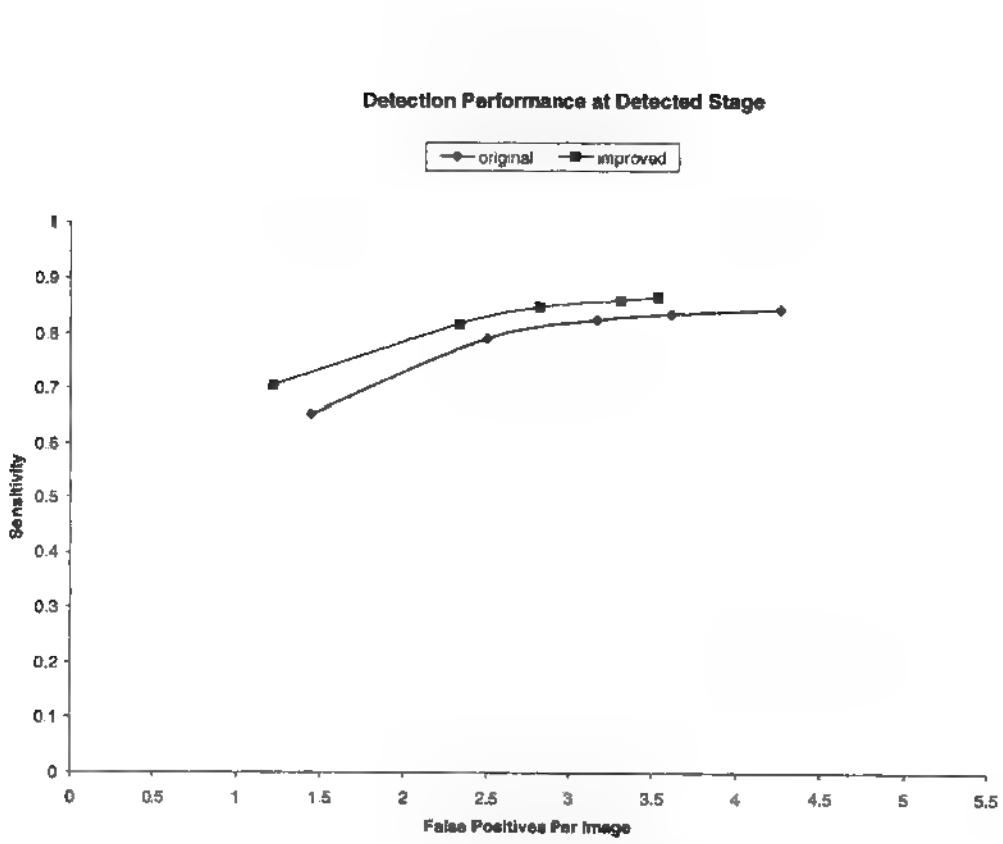


Figure 7. Improvement of CAD cancer detection on mammograms at screening detected stage.

Objective 5: to measure the stand-alone detection sensitivity/specificity of the new CAD system.

Accomplishments:

A new CAD system was designed in the second year research based on our two generations of CAD algorithms for mass detection using digitized mammogram [1][2] and the analysis results of missed cancer in this project. The strategies taken in this new CAD system design include (a) multi-mode detection by breast density classification; (b) breast area partition and region based adaptive detection; (c) weighted classification using the distinguishing features identified in missed cancer analysis.

In order to evaluate the new CAD strategy, it is important to test the sensitivity/specificity and its early cancer detection performance of a radiologist who is assisted by the CAD system and compare it with the performance of single and double reading. For this purpose, large costly trials with several radiologists and a large number of normal cases are required to represent the screening situation. Due to the time and budget limit of this project, before starting such trials, it is important to measure the stand-alone performance of the new CAD system and compare it with existing CAD [1].

Figure 1 and 2 show a comparison of the FROC curves of overall detection performance by new and conventional CAD systems on mammograms at missed and detected cancer stages. More detailed comparisons of detection on mammograms with low (<25%) and high (>25%) density at missed and detected stages are shown in Figure 3-6. It is observed that the new CAD system provides a better detection performance at both missed and detected stages. However, because the new CAD is designed with focus on missed cancer, a bigger improvement is obtained for

missed cancer detection. The improvements on low and high dense mammograms are comparable.

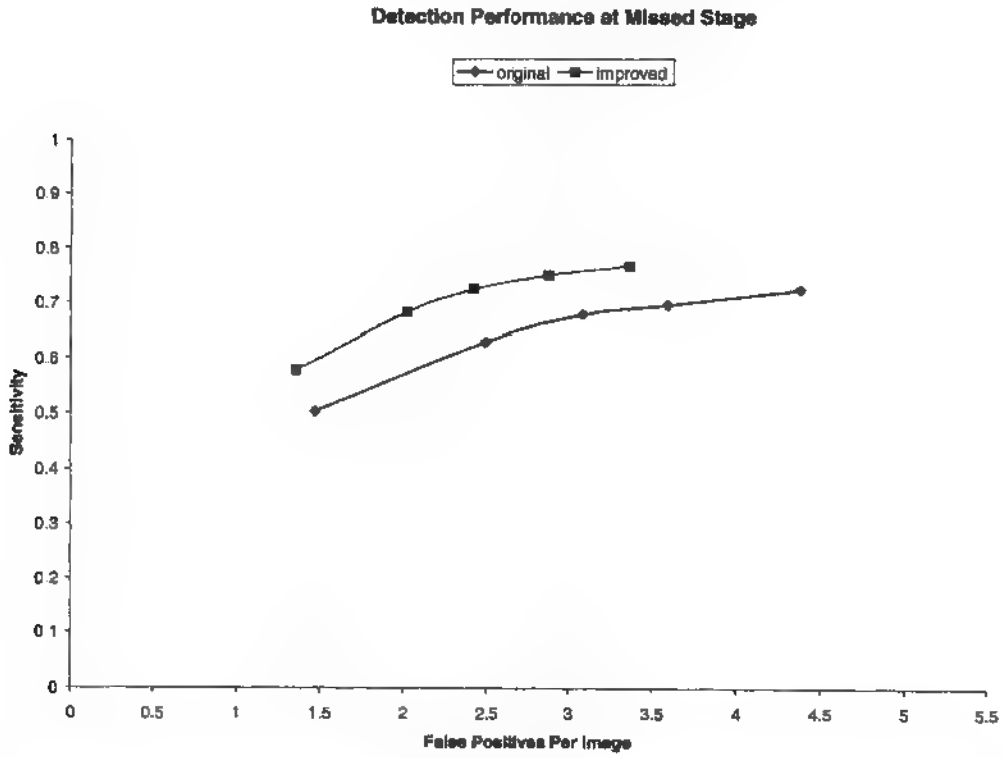


Figure 1. Improvement of CAD cancer detection on mammograms at screening missed stage.

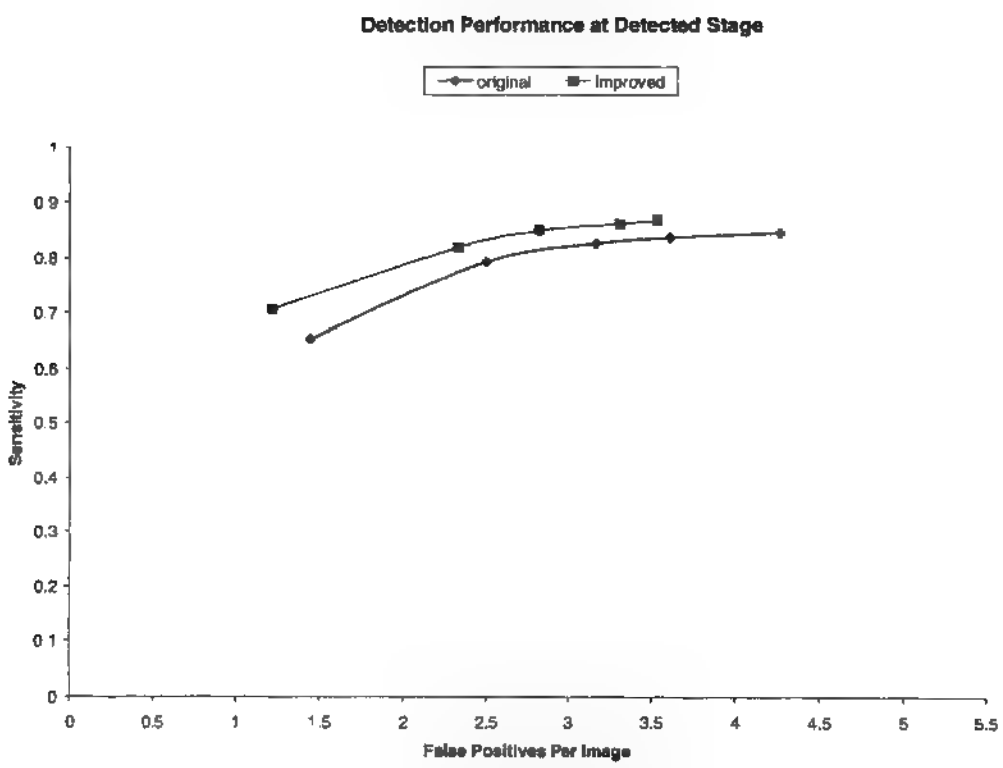


Figure 2. Improvement of CAD cancer detection on mammograms at screening detected stage.

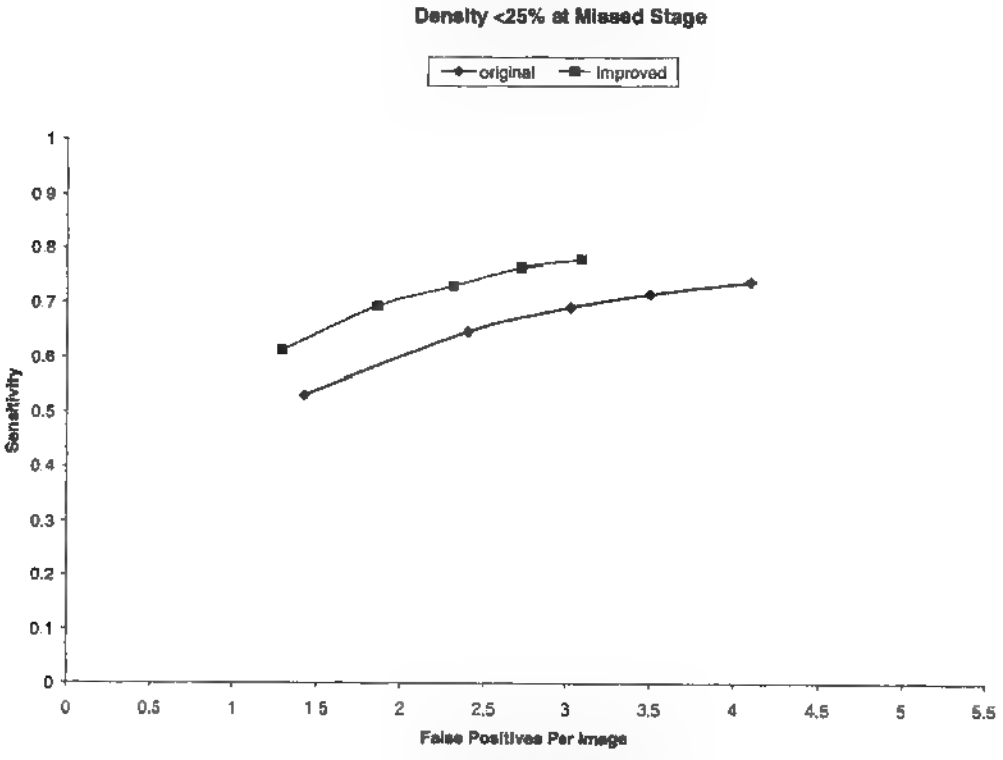


Figure 3 Improvement of CAD cancer detection on low dense mammograms at screening missed stage.

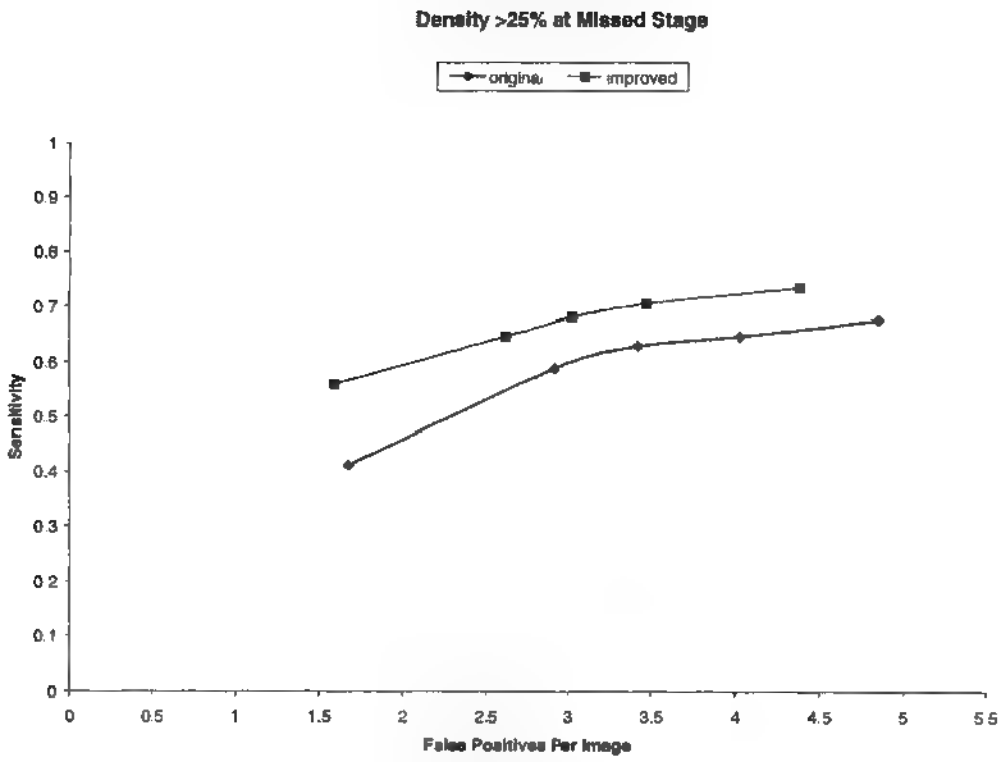


Figure 4. Improvement of CAD cancer detection on high dense mammograms at screening missed stage.

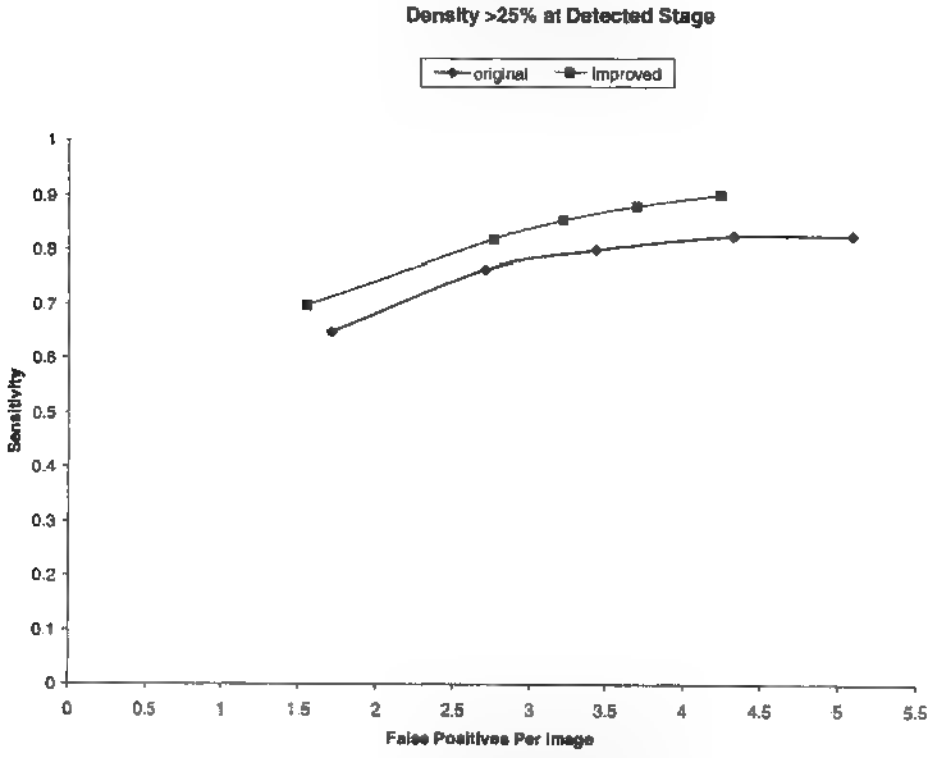


Figure 5. Improvement of CAD cancer detection on low dense mammograms at screening detected stage.

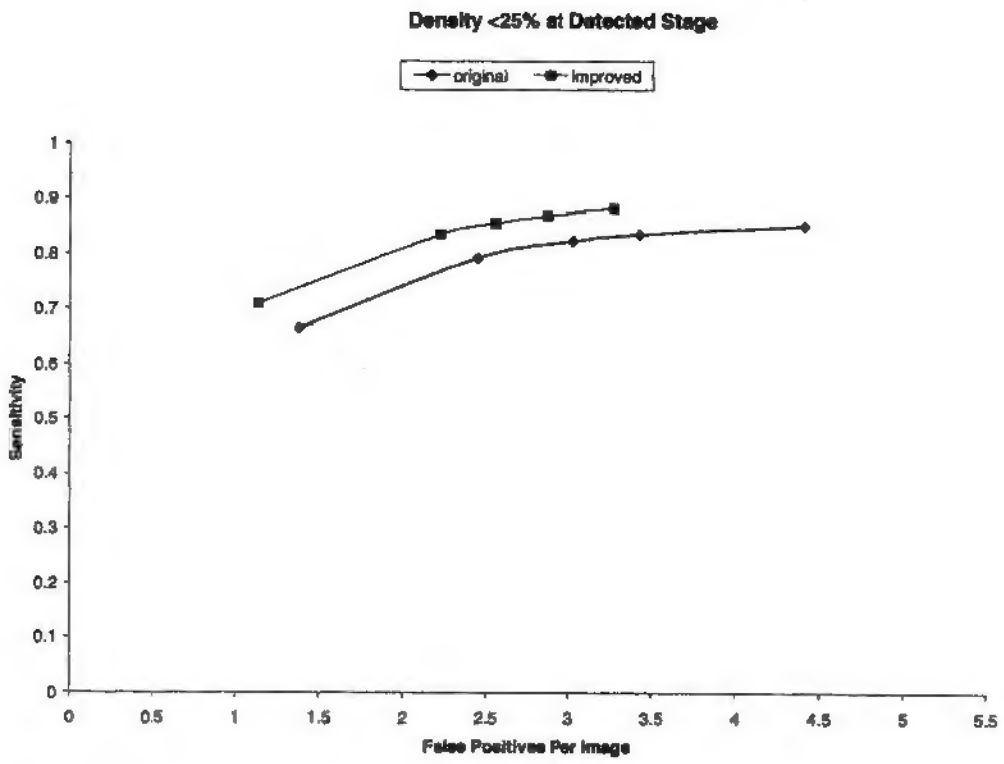


Figure 6. Improvement of CAD cancer detection on high dense mammograms at screening detected stage.

Objective 6: evaluation of early detection

Accomplishments:

An evaluation of early detection by using CAD system was taken. The earliness of detection is measured in terms of the number of months that the cancer is detected by CAD before it is detected by radiologist without assistance of CAD system. Here it is assumed that all true positive detections were accepted by radiologist and there were no negative effects of CAD false positives on decision making in diagnosis.
Figure 7 and 8 present the number of months of early detection at different false positive rates with existing and new CAD systems respectively. It is observed that the cancer could be detected earlier with less false positive signals by using the new CAD strategy.

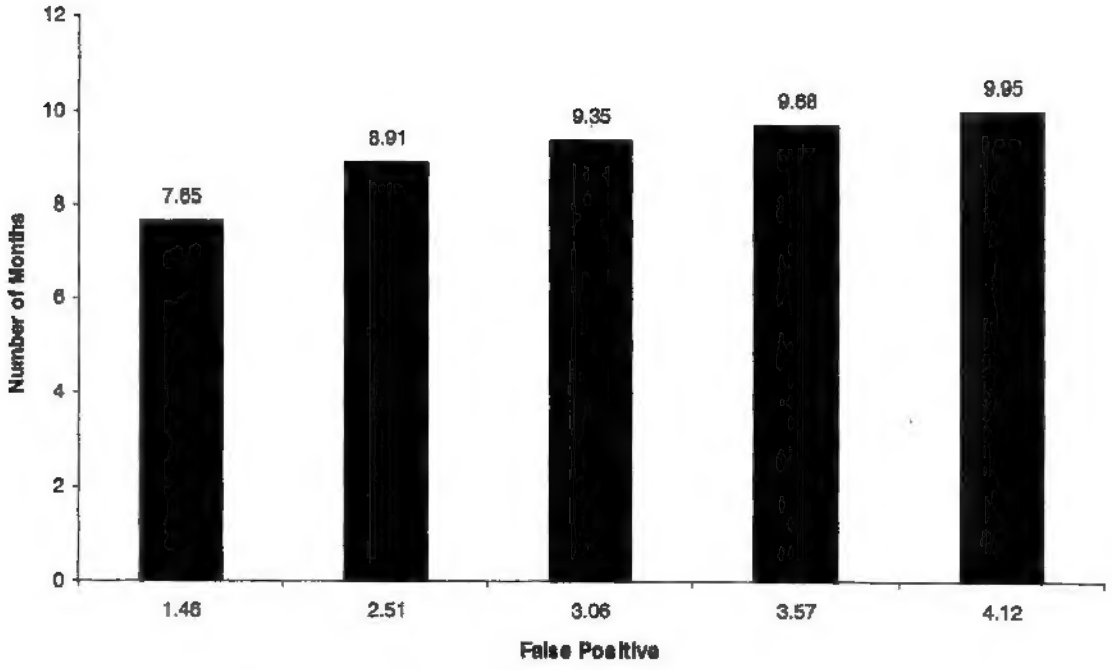


Figure 7. Early detection of cancers with existing CAD system

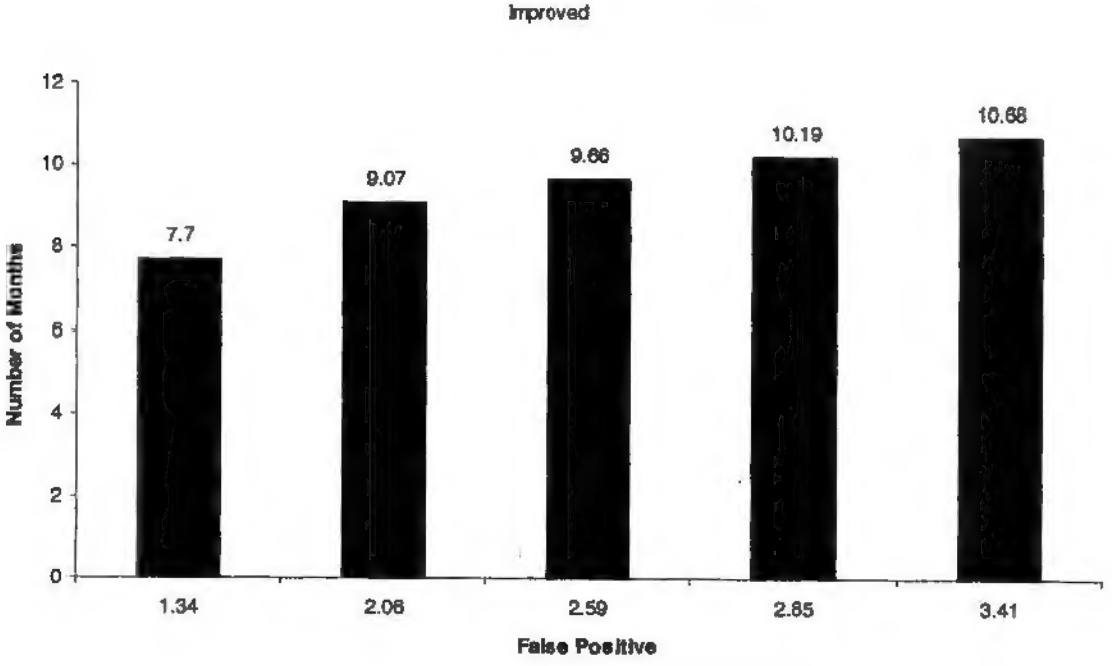


Figure 8. Early detection of cancers with new CAD system

RESEARCH ACCOMPLISHMENTS

1. A database of mammogram was generated containing 86 cases of serial mammograms, which were selected by reviewing 1334 cases. Based on this database, we further generated three datasets, i.e. missed cancer dataset, detected cancer dataset and normal dataset.

2. A series of statistical analyses of the computerized features of missed cancers (false negatives) versus detected ones (true positives) and their interval changes was taken. Based on the test P-values, the features with significant impact on radiologist's diagnosis and that potentially be useful for early detection could be identified.

3. A comprehensive analysis was taken on the effect of breast density on cancer detection. The accomplishments include breast dense tissue segmentation, correlation analysis of mammogram density features between missed and detected stages, statistical testing of density difference between normal and cancerous mammograms, baseline study of the effect of density on CAD detection performance using existing algorithm.

4. A new CAD system was designed based on the existing second-generation CAD algorithm and the missed cancer analysis. Due to the effective modification strategies taken in the new system, detection performance was improved for mammograms at both detected and missed stages. However, with the focus on missed cancer analysis and detection, a bigger improvement was obtained in detecting missed cases even though the general detection performance is still lower than that at detected stage.

5. An evaluation was taken to measure the stand-alone detection sensitivity/specificity of the new CAD system. Comparisons of overall detection performance and the detection on mammograms with low (<25%) and high (>25%) density at missed and detected stages were performed. It is observed that, due to the effective modification strategies taken in the new system, detection performance was improved for mammograms at both detected and missed stages. Because the new CAD system is designed with the focus on missed cancer analysis and detection, a bigger improvement was obtained in detecting missed cases even though the general detection performance is still lower than that at detected stage. The improvements on low and high dense mammograms are comparable.

6. An evaluation of early detection by using CAD system was taken. It is observed that the cancer could be detected earlier with less false positive signals by using the new CAD strategy.

REPORTABLE OUTCOMES

1. Presentation and/or publications

(a) Y. Qiu, L. Li, D. Goldgof, R.A. Clark, "Three dimensional deformation model for lesion correspondence in breast imaging," Proceedings of SPIE Medical Imaging, 2003.
(b) Lihua Li, Zuobao Wu, Zhao Chen, Angela Salem, Maria Kallergi, Claudia G. Berman "Statistical Analysis of Missed Cancer Features in Screening Mammography," Proceedings of SPIE Medical Imaging, 2005.

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[5] L. Li, R.A. Clark, J. A. Thomas "Computer-aided diagnosis of masses in full-field digital mammography," Academic Radiology, 2002; 9.

[6] L. Li, Yang Zheng, Lei Zhang, R.A. Clark, "False-positive reduction in CAD mass detection using a competitive classification strategy," Medical Physics, 28(2), Feb. 2001.

[7] L. Li, R.A. Clark, J. A. Thomas "Computer-aided diagnosis of masses in full-field digital mammography," Academic Radiology, 2002; 9.

[8] L. Li, Yang Zheng, Lei Zhang, R.A. Clark, "False-positive reduction in CAD mass detection using a competitive classification strategy," Medical Physics, 28(2), Feb. 2001.